Pediatric Hypertension Treatment Working Group Meeting
Obstetric and Pediatric Pharmacology Branch
National Institute of Child Health and Human Development
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Best Pharmaceuticals for Children Act (BPCA) Overview

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After thanking attendees for their participation, Dr. Mattison presented an overview of the Best Pharmaceuticals for Children Act (BPCA). He briefly described seminal legislation over the past 30 years that laid the groundwork for BPCA. He noted that during the 1970s and 1980s, the pediatric use of drugs often evolved without any adequate supporting data. Even now, drug development usually focuses on adult pathophysiology, with the hope that direct extrapolation will be valid for pediatric use. Dr. Mattison noted that it is clear that targets may not always be the same in children compared with adults. He emphasized that although it is clear that this issue will be critical in treating pediatric hypertension, the extent or the consequences are not as clear.

Dr. Mattison pointed out several issues related to drug use in treating children:
- There tends to be very little solid information on long-term drug safety in children.
- Safety characterization for pediatrics should be thought of differently than for adults.
- Although there has been considerable research on neurodevelopmental consequences, research should also study drug effects on the development of other organs as well.

Dr. Mattison next described key elements of BPCA of related to this working group:
- It renewed pediatric exclusivity continuing for pharmaceutical manufacturers.
- It provided a mechanism for studying generic or off-patent drugs.
- It fostered interaction among various institutes within NIH, thus enabling direct access to experts in areas relevant to BPCA related to therapeutic design as well as access to clinical populations.

One challenge facing NICHD was to dispel the mistaken assumption that Phase III and Phase IV studies could be undertaken. However, it was found that there was insufficient or poor data, even regarding pharmacokinetics (PK), for many of these drugs.

Dr. Mattison concluded by pointing out that over the past 3 years, working with the U.S. Food and Drug Administration (FDA), other institutes within NIH, and outside experts, NICHD has taken a drug interaction approach. Hypertension and the drugs currently on the list as treatments for hypertension present an opportunity to step back from that perspective. He suggested that this working group would be an ideal forum to begin to take a broader view. That is, that it may be more appropriate to think about the condition in a developmental context as the basis for understanding therapeutic strategies.

Introduction and Objectives

Perdita Taylor-Zapata, M.D., OPPB, NICHD, NIH, DHHS

Dr. Taylor-Zapata welcomed workshop attendees and thanked them for their participation. In reviewing the goals for the meeting, Dr. Taylor-Zapata briefly discussed the evolution of a clear definition of pediatric hypertension, as well as the scope of the condition.

Although it is clear that children do have high blood pressure, the outcomes of the condition are less clear. Dr. Taylor-Zapata pointed to recent studies that have found that hypertensive children have more than a twofold increased risk for cardiovascular disease in adulthood. She cited other studies that reported left ventricular hypertrophy in more than one-third of children and teens with mild, untreated, elevated blood pressure (BP). Dr. Taylor-Zapata explained that in its 2003 report, the U.S. Preventive Services Task Force concluded that the evidence from these and other studies was not sufficient to provide a basis for a recommendation for or against routine screening for pediatric hypertension.

In addition to the lack of clinical guidelines for screening and treating pediatric hypertension, Dr. Taylor-Zapata outlined a number of other issues directly related to defining prevention and treatment protocols for hypertension in children:

- Although the relationship between elevated BP and cardiovascular disease in adults is clear, that relationship is not clear in children.
- Recent clinical trials have demonstrated that effective BP control usually requires two or more antihypertensive agents. The reasons for this effect are not yet known. Also unknown is whether that same effect is true in hypertensive children.
- The publication in December 2004 of the *Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents* provides more data on BP values in children and offers an approach to pediatric screening of elevated BP.

Dr. Taylor-Zapata noted that several key questions remain unanswered:

- What is the safe and effective strategy for treating high BP in children?
- How does the public health community narrow the gap between what is indicated on labels of antihypertensive drugs and how the drug is actually used?
- What are the strategies for preventing pediatric hypertension?

While admitting that these questions are far from being answered, Dr. Taylor-Zapata suggested using them as a basis for the goals of this workshop:

- Discuss the status of clearly defining pediatric hypertension, its associated risks, and the natural history of hypertension in children.
- Identify next steps in defining risk factors and how to convey awareness of those factors to the at-risk population.
- Discuss the role and design of clinical trials; define outcome measures for those studies.
- Determine how to best disseminate information.

In concluding, Dr. Taylor-Zapata emphasized the urgent need to reach these goals.

Scope of the Problem of Juvenile Hypertension: Changing Epidemiology and Implications for Clinical Trials

Jonathan M. Sorof, M.D., AstraZeneca

Dr. Sorof began by noting that although pediatric hypertension has been recognized in children since the 1960s, essential hypertension has become increasingly more prevalent during late childhood and adolescence. It is not clear whether the same risk factors that affect adults also influence essential hypertension in children.

Dr. Sorof presented an overview of completed or ongoing Phase III and Phase IV antihypertensive clinical trials. He explained that the criteria for defining hypertension in children have evolved over the past 30 years. Dr. Sorof discussed the role of number of visits as an indicator of hypertension. A review of these studies indicates that an increased number of visits (and therefore, increased number of BP readings) tends to result in lower BP. Dr. Sorof pointed out that these studies confirm that a single screening is not reliable and that an increased number of visits is necessary to get accurate data.

Dr. Sorof next discussed the Houston School-Based Screening Study, which was a screening for hypertension and obesity at eight Houston urban public schools over a 7-month period. He pointed out that children are similar to adults in both the dynamics and the results of being enrolled in clinical trials. In the Houston Study, obesity was the threshold criterion. The researchers estimated that 1 of every 10 obese children would have persistent hypertension requiring treatment. Dr. Sorof cautioned that there were methodological issues in these studies related to how BP was being measured.

Dr. Sorof summarized the results of a number of recent studies:

- Patients need more than one drug to control hypertension.
- As with adults, it is extremely difficult to lower BP in obese children without using more than one drug.

Dr. Sorof next addressed the issue of ethnic predisposition to hypertension. He explained that the Houston study was conducted in an urban setting among an ethically diverse population. Subjects recruited for the study mirrored the U.S. census breakout for Houston. Results of the Houston study paralleled results of other studies that found no evidence that hypertension is more prevalent in African-American children than in other population groups. However, when controlling for ethnicity and gender, obesity greatly increases the risk for hypertension in children.

Dr. Sorof listed the following conclusions:

- Repetitive screening is essential for accurate diagnosis of pediatric hypertension. It is unclear, however, how long a child should be observed before hypertension is diagnosed.
- Obesity is currently the most common cause of juvenile hypertension. It is still not clear whether it is more appropriate to treat the obesity or the hypertension.

- Systolic hypertension is the most prevalent form of juvenile hypertension. The mechanism involved must be determined, and it must be determined whether that mechanism has implications for choice of drug class.
- Ethnic predisposition for hypertension in children correlates with current trends in obesity in the general population. Researchers need to determine whether these are ethnic or sociological differences.

Dr. Sorof pointed out that the association of obesity with the methodology of measuring BP will have to be addressed to determine treatment protocols for juvenile hypertension.

Mechanisms of Pediatric Hypertension

Julie Rich Ingelfinger, M.D., Harvard Medical School and Massachusetts General Hospital

Dr. Ingelfinger explained that pediatric hypertension is a complex problem with, as yet, no satisfactory solution. She emphasized the need for preventing the effects of hypertension on the cardiovascular system, renal system, and central nervous system. Although the relationship of hypertension to chronic renal disease is well documented for adults, the same relationship seems to exist for children, as well. The long-term effects of untreated pediatric hypertension are still unknown.

Dr. Ingelfinger discussed the factors that control BP. She also discussed the association of hypertension with chronic renal disease, as well as inhibition of the renin-angiotensin system. Dr. Ingelfinger noted the importance of considering the differential effects of angiotensin 1 (AT1) versus those of angiotensin 2 (AT2). She discussed the role of AT2 in chronic renal disease.

Dr. Ingelfinger next discussed oxidative stress in relation to endothelial dysfunction and as a precursor to hypertension and atherosclerosis. Although not readily seen in children, oxidative stress has been found in teenagers and young adults.

Dr. Ingelfinger then discussed how an imbalance in factors such as growth promoters and growth inhibitors affects vascular tone and structure. She explained that although these mechanisms are not clearly understood, it is clear that renal disease is directly related to increased risk of hypertension and that hypertension is associated with increased risk of renal disease.

Dr. Ingelfinger emphasized that primary hypertension is currently considered a syndrome with no known cause. She described the effects of obesity (including insulin resistance and altered vascular reactivity) that are directly related to increased risk of hypertension. She discussed findings from a study of obesity in hypertensive adults, which found that subjects with even borderline hypertension were at increased risk of becoming obese.

Dr. Ingelfinger summarized findings from a recent study that delineated factors associated with obesity and how those factors are associated with hypertension

- Increased renin-angiotensin activation
- Increased amounts of leptin
- Increased sympathetic activation

- High levels of sodium chloride reabsorption, which leads to volume expansion
- High levels of intracellular pH and sodium, leading to increased vascular smooth muscle cell proliferation.

Dr. Ingelfinger explained that increased vascular smooth muscle cell proliferation leads to increased peripheral resistance, which is directly linked to hypertension. Increased volume expansion due to high salt reabsorption is also directly linked to hypertension.

In concluding, Dr. Ingelfinger emphasized the need to delineate the mechanisms in developing organisms that predispose a child to hypertension. She suggested that delineating the mechanisms involved in obesity and hypertension may be the key to preventing both conditions.

Use of Off-Patent Antihypertensives in Children

Joseph T. Flynn, M.D., M.S., Children's Hospital, Montefiore Medical Center

Dr. Flynn began by reminding participants that as recently as 5 years ago, the only pediatric information available for many antihypertensive medications was that the "safety and effectives in children" had not been determined. Dr. Flynn noted that this statement was an indicator that there were few studies of antihypertensive medications in children until passage of the Food and Drug Administration Modernization Act (FDAMA) in 1997. He pointed out that since enactment of FDAMA, more than 300 written requests (WRs) and numerous pediatric trials have been undertaken. Antihypertensives are one of the most commonly studied drug categories.

Dr. Flynn presented a list of studies of antihypertensives of interest to BPCA. He indicated the status of each study and discussed the issues of exclusivity and labeling. Dr. Flynn summarized changes that have occurred due to FDAMA:

- BP reduction has been the only primary endpoint in determining efficacy.
- Because of the short duration of most trials, safety information has been limited.
- Labels have been changed for enalapril, fosinopril, lisinopril, amlodipine, fenoldopam, benazepril, and losartan.

Dr. Flynn explained that BPCA requires that FDA issue WRs for pediatric studies of agents with potential health benefit to children and that no longer have patent protection or marketing exclusivity. He noted that as of February 2005, FDA has issued 10 WRs; however, nitroprusside is the only antihypertensive included.

Dr. Flynn discussed the potential impact of BPCA on hypertension treatment and prevention:

- Many other antihypertensives are currently being used in addition to the few with WRs.
- Most of these drugs no longer have patent protection or marketing exclusivity.
- How these drugs are being used to treat hypertension in children is unknown.

Dr. Flynn described a 2001 fax survey of pediatric nephrologists. Of the 438 physicians surveyed, 190 responded to questions on BP measurement techniques, BP treatment goals, and choice of antihypertensive medications. Survey results indicated that:

- Preferred medications for treatment of primary and secondary hypertension in children are mostly chosen from drug classes in which agents with pediatric data/labeling are available.
- Second-line medications are chosen from drug classes in which agents may not have pediatric data/labeling.

Dr. Flynn next reported on a May 2005 follow-up e-mail survey:
- Of the 112 physicians who responded, 108 indicated that they commonly prescribe drugs that are off-patent or do not have labeling information specific to pediatric use.
- Some commonly chosen classes of medications have agents with pediatric efficacy and safety data, but other chosen medications do not.
- Off-patent oral agents commonly used and that deserve further study include atenolol, hydrochlorothiazide (HCTZ), extended-release nifedipine, and labetalol.
- Off-patent agents administered intravenously that are commonly used and merit further study include nitroprusside, labetalol, and hydralazine.

In closing his presentation, Dr. Flynn emphasized the need for well-conducted studies of off-patent antihypertensives in children. He argued that these studies will lead to improving the treatment of pediatric hypertension.

Pediatric Hypertension Treatment Clinical Trials Designs

Mark Schreiner, M.D., Children's Hospital of Philadelphia

Dr. Schreiner discussed designing and conducting pediatric hypertension trials, including the benefits and disadvantages of several design models:
- **Trial A: Parallel Group with Placebo.** The design of this model is simple; negative data can be interpreted readily. However, this design presents the potential for inadequate treatment for placebo and lower dosages; high dosages may cause hypotension. These risks are considered too significant for patients with renal-vascular hypertension.
- **Trial B: Parallel Group without Placebo.** Like trial-A design, this model is simple, and it avoids the problem of nontreatment. There is, however, the potential for inadequate treatment for placebo and lower dosages. As with trial-A design, high dosages may cause hypotension. Because of omission of placebo, negative data cannot be interpreted.
- **Trial C: Parallel Group with Randomized Withdrawal.** In this complex model, all subjects are treated; negative findings can be interpreted; and exposure to placebo is minimized. A major disadvantage of this model is the potential long period on inadequate treatment. As with the previous two models, the trial-C model may lead to hypotension.
- **Trial D: Forced Titration with Randomized Withdrawal.** As with trial C, all subjects receive treatment; exposure to placebo and inadequate treatment are minimal. However, this model is based on a complex design. Titration is required, even if BP is controlled with lower dosage.

Dr. Schreiner noted that withdrawal designs are complex, and they usually require a considerable length of time for BP to reach baseline.

Next, Dr. Schreiner described the design model used, as well as the inclusion and exclusion criteria of two studies of angiotensin converting enzyme (ACE) inhibitors. He summarized lessons learned from each study:

- **Study 1.** The PK aspect of the study was completed after the trial began. There was poor enrollment for 2 years, and the trial failed to show a dose-response relationship during randomized withdrawal (high dose was more effective than placebo).
- **Study 2.** This trial incorporated new FDA requirements based on the 2001 WR. Additional study sites were included. The monitoring burden was increased, which significantly increased financial cost of the trial. During dose escalation, 166 subjects (54 percent) had at least one adverse event (AE). However, only six subjects had an AE of severe intensity; three subjects had treatment-related AEs. During randomized withdrawal, 82 (38 percent) subjects had at least one AE; of those, two were AEs of severe intensity. Although 11 subjects had an AE that was possibly related to the study drug, no subject had an AE that could be definitely attributed to the drug. Moreover, no subjects discontinued participation due to an AE.

Based on experience from these studies, Dr. Schreiner offered the following suggestions when considering designs for future clinical trials:

- Analyze PK data before beginning an efficacy study.
- Use a wide range of doses to assess dose-response relationships.
- Ensure that the randomized withdrawal period is sufficient to allow for return to baseline in trial-C and trial-D designs.
- Avoid trial-B design. Use of a placebo is essential for determining assay sensitivity and assessing safety.
- It is safe to limit enrollment to subjects with BP less than 20 mmHG above the 96th percentile.
- Consider using simpler study design.
- Be aware of the 2004 National High Blood Pressure Education Program treatment guidelines.

In closing, Dr. Schreiner noted that trial-A design may be preferred when studying patients with stage I hypertension. He recommended using liquid preparations when studying young children. Dr. Schreiner reiterated the need for neurocognitive testing that would accommodate age, language, and cultural differences.

Recruiting Pediatric Subjects for Antihypertensive Clinical Trials

Donald L. Batisky, M.D., Children's Hospital, Ohio State University

Dr. Batisky began by outlining barriers to recruiting subjects for pediatric clinical trials:

- The study population consists of infants, children, and teenagers.
- Study protocols are often unfriendly to children and teenagers.
- Clinical operations tend to be conducted in a cumbersome infrastructure; clinical studies usually are not advertised, leading to a lack of "buy-in" among the targeted local population.

Dr. Batisky argued that there are several basic strategies to help ensure successful clinical trials:

- Begin with a scientifically sound protocol.
- Conduct the study within an appropriate and strong infrastructure.

- Ensure that the clinical trials are embraced by clinical practice.
- Ensure that clinical practice is enhanced by the clinical trial(s).

Dr. Batisky next shared his experiences in recruiting pediatric subjects. He noted that individual subjects were identified during clinic visits and from referrals from other clinicians. Subjects were also identified from records in the hospital pediatric nephrology database.

Dr. Batisky suggested that an important first step in structuring a clinical trial is to plan—that is, establish a system and infrastructure (for example, an online database) to store information that can be searched when recruiting patients. He briefly described the Pediatric Clinical Trials International (PCTI) database at Children's Hospital in Ohio. First established 20 years ago, the PCTI database is HIPAA-compliant and currently houses data from clinical trials conducted at Children's Hospital. As of spring 2005, 14 hypertension trials have been completed; another 6 trials are ongoing. These trials are studying the safety/efficacy and PK of numerous ACE-inhibitors and calcium channel blockers.

Dr. Batisky pointed out that study subjects are also the researcher's patients (or become patients as a result of enrollment in the study). This dynamic raises the issue of consent/assent; when the study ends, the subject is still a patient.

Participants discussed the issue of how to deal with a subject who responded successfully to the study drug after the study is completed. Participants agreed that study subjects should do as well as or better than patients who did not participate in the study. That is, a subject who responded to a study drug should continue on that drug after the study has been completed. Moreover, participants also agreed that well-designed clinical studies should reflect current, sound clinical practice, which in turn, should inform future clinical guidelines.

Discussion Session

At the conclusion of presentations, participants identified a number of issues that they discussed in detail. These issues included:

- How to determine drug effectiveness without compromising clinical outcomes. The issue is not whether a drug works in most cases but rather whether the drug works in the clinician's patient.
- Overall goal of these studies. BPCA intent is to determine whether there is basic pharmacological evidence that points to a treatment baseline and a point at which the dosage is considered dangerous for children.
- Purpose of labeling counterbalanced with scientifically sound studies, the results of which can be disseminated to clinicians.
- Labeling content.
- Impact of intervention. The current assumption (perhaps misinformed) is that treating hypertensive children will improve health outcomes in adulthood.
- Need for hypothesis-generating studies.
- Strategies for increasing buy-in for a study among clinicians.
  - A compelling study question

  - A novel study question
  - Study purpose expanded beyond determining whether a specific drug (or specific dosage) works in that patient population.
- Adequacy of per-patient compensation
- Developing an "ALL-HAT" approach that examines partnerships with private entities and pharmaceutical firms
- Defining and recommending new surrogate markers such as:
  - Lipid profiles
  - Uric acid
  - Calcium excretion
  - Bone density
  - Cardiac function
  - Arrhythmias
  - Central nervous system effects
  - Microvasculature patterns in the extremities
  - Vascular reactivity
  - Tibia height/bone growth
- Importance of differentiating surrogate markers of safety from efficacy markers
- How to ensure that changes in drug labeling inform clinical practice
- Mechanisms for disseminating study findings and changes in drug labeling information.

Participants discussed options for design of clinical trials, including a randomized trial based on JNC-7 guidelines. Although this model will be inexpensive and effective, participants questioned the long-term benefits for patients.

Another option discussed was a three-party study model. This approach would incorporate a short-term trial-A model with titration to goal. It would allow for additional drugs for those children who did not respond to the treatment model. Participants acknowledged that this approach would include baseline, as well as periodic, assessments. It would answer questions regarding effective dosage and whether a single agent or combination of agents is the preferred protocol.

A third option suggested was to conduct two studies: one would use a drug that already has pediatric labeling along with a thiazide. The second study would recruit subjects that are currently on monotherapy and then include a thiazide as a second therapy. Study design would include stratified randomization, with one-third of subjects taking a medication from one drug class, one-third taking a medication from a second drug class, and another one-third taking medication from a third drug class. Participants agreed to adding a thiazide, if that is current clinical practice.

Participants considered obesity as a confounder. They discussed the possibility of a two-arm design for a study of obesity versus a study of hypertension. They identified the following issues:
- Need for ongoing monitoring (for example, case report forms, data monitoring)
- Ethnic differences
- Age as a surrogate marker for hypertension

- Need for differentiating and documenting primary versus secondary hypertension
- Ensuring patient safety
- Possibility of revising study criteria to accommodate young children with primary hypertension.

Before concluding this session, participants discussed the process for preparing and announcing funding opportunities to conduct BPCA-funded studies. They discussed various mechanisms (for example, using already-established, credible networks) to "streamline" the process so that studies could be expedited.

Before adjourning the workshop, Dr. Taylor-Zapata thanked participants for their informed input and commitment. She emphasized that although BPCA initially focused on drug indications, it leaves room for drug-to-drug comparisons and for studying long-term consequences of a disease or condition. She assured them that their knowledge and experience would be invaluable in developing next steps for determining BPCA-funded studies, particularly studies of hypertension in children.

Workshop participants briefly discussed current actual clinical practice. They agreed that most physicians currently are using a combination of calcium channel blockers and ACE-inhibitors as the preferred treatment for pediatric hypertension.

Participants

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